Aspects of the epidemiological chain of bovine neosporosis and applications as a prophylaxis tool

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1 INTRODUCTION

Systemic parasitic infections are responsible for serious losses in agriculture. In the reproductive sphere of cattle farming, bovine neosporosis is described as one of the main diseases causing abortions in cattle herds, generating considerable reproductive and, consequently, economic impacts in the Brazilian livestock sector. This disease is caused by the protozoan *Neospora caninum*, a coccidian found in the form of tissue cysts and intracellular tachyzoites. This condition gives the parasite an efficient capacity for dissemination and transmission within cattle herds, and can infect up to 90% of animals in confinement with dairy or beef aptitude (DUBEY et al. 2006).

The protozoan *Neospora caninum* was first described in 1988, in Norway, affecting puppies, whose species is described as the definitive host of the protozoan. In Brazil, the first report of neosporosis was made in 1999, in the state of Bahia. Since then, from serological studies, the disease has been reported endemic in several regions of the country, such as Bahia, São Paulo, Rio Grande do Sul, Paraná, Mato Grosso do Sul and Minas Gerais (ANDREOTTI et al., 1999; CORBELINI et al., 2000; LOCATELLI-DITTRICH et al., 2001).

The biological cycle of *Neospora caninum* is heteroxenous, and the domestic dog of the subspecies *Canis lupus familiaris* is described as the usual and definitive host of the parasite, and may also affect several intermediate hosts such as horses, ruminants, humans, foxes (*Vulpes vulpes)* and wild rats (*Rattus novergicus)***.** In some cases, although not well elucidated, the dog can assume the role of intermediate host (OSHIRO, 2006; LLANO, 2013). Besides the domestic dog, the coyote (Canis *latrans)*, the wolf (Canis *lupus)* and also the dingo (*Canis lupus dingo)* can be considered definitive hosts. In addition, greater attention should be paid to neosporosis, since not only animals but also humans can be equally affected and this disease is therefore a public health issue. Indirect immunofluorescence (IFI) techniques were used in humans, which were positive for anti-N. *caninum*

antibodies and negative for *T. gondii* antibodies, suggesting that the disease can be considered zoonotic (TRANAS et al., 1999).

Fundamentally, there are two forms of transmission of neosporosis that determine the spread between herds, which can occur horizontally through the consumption of water or food contaminated with oocysts from dogs or other infected canids; or vertically, where transplacental transmission occurs. It is important to point out the importance of endogenous transplacental transmission in maintaining the disease in herds, since about 95% of seropositive cows will abort or generate seropositive calves (DINIZ et al., 2019; MCALLISTER, 2016).

In addition, it is important to note that the economic losses caused by *Neospora caninum* are related to disorders of the reproductive system, which mainly include disorders such as return to estrus, with regular or irregular intervals, abortions, birth of weak and non-viable animals, with neurological signs or even in the condition of persistently infected (ALMERIA et al.,2009a; ALMERIA et al., 2010; DUBEY, SCHARES AND ORTEGA-MORA, 2007). Barros et al. (2014) reported that the losses caused by neosporosis have different proportions, according to the technological level of the rural enterprise and with negative consequences for the economy of the State.

The main clinical sign related to the infection of adult females is abortion, which is more frequent between the fifth and sixth month of gestation. In neonates, neurological changes, stillbirths, mummification, malformations, myocarditis and also polymyositis can be observed. If it occurs in the final period of gestation, delivery will occur normally, but the calf may be congenitally infected, and this infection may be repeated in future generations (GUIMARÃES, 2007).

The disease is controlled by correct and accurate diagnosis, which can be done by laboratory tests such as immunohistochemistry, histopathology and polymerase chain reaction. Also, the method of isolation of the parasite in cell cultures can be used. It is important to note that serological methods stand out from the previously described tests, as they are a valuable tool used in longitudinal and cross-sectional epidemiological studies. Several serological tests, including ELISA, RIFI, TAD can be used to identify anti-Neospora antibodies in serum and cavitary fluids (DUBEY, 1999). Studies of seroprevalence of neosporosis indicate that the parasitosis is endemic in the national territory and, therefore, may not be easily perceived by the rural producer; it is necessary to awaken him to the economic losses caused by the disease, as well as the need to adopt economically viable control strategies for the rural enterprise.

2 OBJECTIVE

Thus, the general objective of the work was to analyze, from the literature, the economic and reproductive impacts caused by *Neospora caninum* in infected herds. The specific objectives were to describe and point out the importance of prevention and knowledge about the biology and

epidemiology of the etiological agent of bovine neosporosis, in order to subsidize effective prophylaxis measures in rural properties.

3 METHODOLOGY

The present study was carried out based on an exploratory bibliographic research with the scientific databases SciElo, PubMed, CAPES, LILACS, MEDLINE and Google Scholar. For the research, the time frame of publications made between 2003 and 2020 was used, using the following keywords: dogs, neosporosis, abortion, cattle, reproduction, *Neospora caninum,* epidemiology, diagnosis, veterinary medicine and protozoa.

Articles that presented the theme of bovine neosporosis were included in the study, totaling 17 selected articles. Based on the material collected, a qualitative analysis was made of the selected articles, in order to try to highlight the risk factors, economic impacts, epidemiology of the disease and its prophylaxis, as well as the recognition of infected animals and the importance of diagnosis for the control of infection in herds.

4 DEVELOPMENT

Since its description, *Neospora caninum* has been identified in much of the world as an important causative agent of abortion (DUBEY; LINDAY, 1996). However, the inclusion of this protozoan in bovine health control programs, as well as the attribution of clinical or subclinical disease to this parasite, remained for some years without proof and elucidation. This reality may be associated with the late description of the parasite, which is why it is very commonly confused with *Toxoplasma gondii* due to the close phylogenetic relationship between these two parasites. After the description, the international taxonomy committee classified the neosporosis agent as belonging to the phylum *Apicomplexa*, class *Sporozoa,* order *Eucoccidiorida,* suborder *Eiomeriose,* family *Sarcocystidae* and subfamily *Toxoplasmatinae* (OSHIRO, 2006).

The life cycle of *Neospora caninum* comprises three evolutionary stages: bradyzoites, tachyzoites and sporozoites. The bradyzoite forms (from the Greek *bradys*, meaning slow multiplication) are ovoid, represent the latency period and have a decelerated multiplication. At this stage, the parasite is able to form tissue cysts. The cysts are usually oval, lunar or globular in shape, measuring about 107 µm in diameter and are found in the cells of the nervous system. *Tachyzoites* (from the Greek *tachys*, meaning rapid multiplication) are rapidly multiplying, moon-shaped, measuring about 6.0 µm in length. They can be found in nerve cells, macrophages, renal tubular endothelial cells, fibroblasts, hepatocytes and in various tissues of diseased animals. Tachyzoites and tissue cysts are found intracellularly in intermediate and definitive hosts (DUBEY et al., 2002a). Bradyzoites are ovoid, represent the latency period and have a decelerated multiplication, in this period

the parasite is able to form tissue cysts. Cysts are usually oval, lunar or globular in shape, measuring about 107 µm in diameter and are found in cells of the nervous system. Tachyzoites and tissue cysts are found intracellularly in intermediate and definitive hosts (DUBEY et al., 2002a). Oocysts constitute the environmentally resistant form of the parasite. Each oocyst has two sporocysts inside, each with four sporozoites, which are the result of gametogonic sexual multiplication, which occurs in the process of enteroepithelial infection in dogs (WILLIAMS et al., 2009).

Neospora caninum has a facultative heteroxene cycle. This means that the parasite can complete its cycle only in the definitive host, or it can have several intermediate hosts. Thus, contamination covers different species within properties (ORTEGA-MORA et al., 2007). Bovine neosporosis can be transmitted from mother to child by transplacental route, which is called vertical transmission or congenital infection. This is considered the major source of infection, as it can occur more than once in the same animal and through progeny over many generations (ANDERSON et al., 2000). Another way of infection is horizontal transmission also called postnatal infection, where intermediate hosts ingest tissues infected with cysts or food and water contaminated with sporulated oocysts of *Neospora caninum*. When these reach the stomach of the intermediate host, a rupture will occur by mechanical action, resulting in the release of sporozoites in the intestine. These will move to the tissues where asexual multiplication will take place, generating mobile tachyzoites, which will initiate an intense increase of protozoa in a short period of time. Through the bloodstream they spread to different tissues such as: gravid uteri, hepatocytes, vascular endothelium, cardiac muscle, renal cells, alveoli, and placental appendages, in these tissues the tachyzoites cause cell destruction resulting in an acute infection (MCALLISTER et al., 2016).

To understand the epidemiology of *Neospora caninum* it is important to know its prevalence and geographical distribution (DUBEY et al; SCHARES et al; ORTEGA-MORA et al., 2007). Several countries have already confirmed neosporosis in their herds such as Africa, United States, Germany, Mexico, Brazil, among others. Serological studies have been carried out in several regions of the country, such as Bahia, São Paulo, Rio Grande do Sul, Paraná, Mato Grosso do Sul and Minas Gerais (ANDREOTTI et al., 1999; CORBELINI et al., 2000**;** LOCATELLI-DITTRICH et al., 2001).

In Brazil the prevalence of 14.09% among dairy cattle in Bahia was highlighted (GONDIM et al., 1999). In the South region studies show that about 23% of herds with a history of abortion tested positive for *Neospora caninum* infection, the rates reach almost 25% of seropositivity when positive animals without a history of abortion are joined. In Minas Gerais seroepidemiological studies show a relevant variation between regions, the seroprevalence of the parasite ranges from 6.8% to 91.2%. In addition, the protozoan was detected in 81.8% of fetuses examined by immunohistochemistry (CORBELLINI et al., 2002). It is worth noting that the prevalence is variable and depends on the type of sampling used and the laboratory techniques employed.

The Amazon was considered a neosporosis-free region, studies carried out in the state found a prevalence of 8.8% in cows and 72% among farms (AGUIAR et al., 2006). These studies are of paramount importance in epidemiology, because in this way it is possible to have more information and infection rates of the disease. Some states did not register the presence of infection, one of the reasons is usually the lack of serum and epidemiological studies, which ends up hindering the epidemiological reality of *Neospora caninum* in Brazil and the identification of infected females, which are responsible for the proliferation of the parasite through endogenous and vertical transmission routes. Studies show that approximately 95% of seropositive cows will abort or produce infected calves (DINIZ et al., 2019; MCALLISTER, 2016).

Neospora caninum-induced abortions often occur between 5 and 6 months of gestation (ANDERSON et al., 1991; WOUDA, 1998). In this period the fetus is not able to recognize pathogens and becomes more susceptible to infection. In the initial third of pregnancy, the bovine fetus does not recognize pathogens, being vulnerable to *Neospora caninum* (BUXTON et al., 2002). Abortion can occur sporadically, endemic or epidemic, at any time of the year (DUBEY, 2003; GARCIA, 2003; LLANO, 2013). Some signs that can also be observed are the death of the fetus in utero, mummification, autolyzed fetuses, post-birth death, or birth with the chronic form of the disease, which does not present clinical signs, but is extremely worrying because the animal has the ability to transmit the infection and infertility. Fetuses may die in utero and be reabsorbed, mummified, aborted, born dead or born alive but chronically infected (DUBEY; LINDSAY, 1996).

Infected females most often have a high number of antibodies that act against the parasite, but it is important to emphasize that this fact does not represent maternal protection. The bovine fetus is not able to mount an immune response against pathogens before 100 days of gestation (MALEY et al., 2003). This increase in antibodies means a higher rate of passage of *Neospora caninum* through the placenta of the cow, damaging the fetus and thus causing abortion. Usually infected cows do not show any other clinical signs, besides these of reproductive character (ALMERIA et al., 2010).

The diagnosis of bovine neosporosis is based on a number of factors. It is necessary to associate the history of the herd in partnership with the clinical signs presented and laboratory data. Abortion is the most relevant clinical sign presented in old animals, in young animals the appearance of neurological signs and polymyositis is observed. Direct methods detect forms of the parasite or parts of it, such as antigenic substances, while indirect methods depend on clinical, immunological and biochemical evidence that is associated with infection (LINDSAY; DUBEY, 2020; CALLEFE et al., 2021). Laboratory confirmation occurs through histopathological and immunohistochemical examinations in tissues or aborted fetuses. Serological methods such as ELISA, RIFI and NAT are used, with RIF being the most indicated because it has a higher performance among the three. Some authors such as Hasler et al. (2006) warn that caution should be exercised when using ELISA, as it

may present false-negative or false-positive results. Another method used is the molecular method, where the Polymerase Chain Reaction (PCR) is widely used. PCR is a very sensitive method and extremely assertive in the diagnosis of *Neospora caninum.* This technique is mainly applied in the post-mortem diagnosis of neosporosis in fetal tissues (SUTEU et al., 2010). Annual economic losses due to neosporosis reach hundreds of thousands of dollars per year worldwide (DUBEY, SCHARES AND ORTEGA-MORA, 2007).

Control of the disease is difficult because there is no vaccine or specific treatment. Some ongoing studies show that an inactive vaccine may help prevent vertical transmission, but it is worth noting that there has been no confirmation of its efficacy and the subject is still the subject of much debate. There is a growing demand for an efficient vaccine to prevent abortions in cattle and to prevent the excretion of oocysts in definitive hosts (CERQUEIRA-CÉZAR et al., 2017).

Considering that the major form of transmission of the disease occurs vertically, one way of prevention would be the use of serological screening in heifers and cows, in order to identify seropositive animals in the herd, thus being possible to discard contaminated animals and replace the herd using seronegative animals, minimizing the rate of cases present in the property and losses due to abortions. Seropositive cows have a high risk of abortion and there is a high probability of congenital infection in calves born to these animals (MOEN et al., 1998). Another form of contamination occurs through contact of sporulated oocysts with intermediate hosts. Therefore, it is extremely important to prevent or control the presence of dogs in the same environment as the animals. From an epidemiological point of view, it is also important to perform serology on dogs on the property (KATO, 2009).

Domestic dogs should not be fed raw meat and should be prevented from feeding on dead animal carcasses and fetal tissue remains, this type of material should be collected from the environment. The responsible destination of carcasses and placental remains, which should be buried or incinerated, significantly impacts the control of neosporosis (MEGID et al., 2016). The best way to prevent and control the disease is to perform seroepidemiological analysis and to know the reproductive history. The purchase of animals proven negative for *Neospora caninum* is an important form of prevention (DUBEY, SCHARES AND ORTEGA-MORA, 2007).

5 FINAL CONSIDERATIONS

Neosporosis is one of the main diseases that affect the herds of several countries. Being considered the biggest cause of abortions in Brazil, it is majestic that greater attention is paid to it, which is often neglected by both rural producers and veterinarians. Its impact goes beyond pathologies and also directly affects the economy. Biosafety measures should be used in sanitary, reproductive,

nutritional and facility management along with prophylaxis to have a real control and then end the disorders caused by bovine neosporosis.

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